REMARKS

Claims 205-231 are pending in the application. Claims 205-209 and 219-223 are withdrawn as being drawn to non-elected inventions. Claims 210-217 and 224-231 are under consideration. Claims 205, 213, 215-217, 224-226, 229-231 have been amended to further clarify the intended subject matter of the claimed invention. Entry of these amendments is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Comments Regarding Restriction Requirement

Applicants affirm the election with traverse of claims 210-217 and 224-231, corresponding to the invention of Group II, and the election with traverse of SEQ ID NO:64. Applicants reiterate their request that the Examiner withdraw the Restriction Requirement at least with respect to claims 205-209, and examine those claims together with the elected polynucleotide claims of Group II. Applicants believe unity of invention exists for claims drawn to the polypeptide sequence of SEQ ID NO:12 (*i.e.*, claims 205-209) and claims drawn to the elected polynucleotide sequence of SEQ ID NO:64 which encodes SEQ ID NO:12 (*i.e.*, claims 210-214, and 217) based on the rules concerning unity of invention under the Patent Cooperation Treaty. The Administrative Instructions Under The Patent Cooperation Treaty, Annex B, Unity of Invention, Part 2, "Examples Concerning Unity of Invention" provide the following guidelines with regard to unity of invention between a protein and the polynucleotide that encodes it:

> *Example 17*
> Claim 1: Protein X.
> Claim 2: DNA sequence encoding protein X.
> Expression of the DNA sequence in a host results in the production of a protein which is determined by the DNA sequence. The protein and the DNA sequence exhibit corresponding special technical features. Unity between claims 1 and 2 is accepted.

The rules under MPEP section 1893.03(d) require the Examiner to apply the Unity of Invention standard PCT Rule 13.2 instead of U.S. restriction/election of species practice in national stage applications, such as the instant application filed under 35 U.S.C. 371.

Claim 218 has been canceled and claims 205, 217, and 224 have been amended in view of the sequences disclosed by Strausberg et al. (GenBank Accession Number AA806217) and Morgan et al. ((GenBank Accession Number AJ009985). As currently pending, the claims drawn to polynucleotides and the claims drawn to polypeptides do not encompass prior art, and the "objection of lack of unity" based on prior art no longer applies. Therefore, Applicants again request that the Examiner withdraw the Restriction Requirement, at least with respect to claims 205-209, and examine those claims together with the elected polynucleotide claims of Group II.

Objections to the Specification

Title

The Examiner objected to the title of the specification on the grounds that it is allegedly not descriptive of the invention to which the claims are directed (Office Action, page 3). As mentioned above, Applicants believe that claims drawn to the polypeptides of the invention, according to the unity of invention standard, should be examined with the elected claims drawn to the polynucleotides currently under examination. Upon allowance of the claims under examination, Applicants will consider revision of the title as requested by the Examiner. Until then, such revisions would be premature.

Hyperlinks

The Examiner also objected to the presence of references to hyperlinks and/or other forms of browser-executable code in the specification (Office Action, page 3). Applicants did not intend to have active links in the specification, nor to incorporate the subject matter of websites by reference to such hyperlinks. Applicants have amended the specification to remove active hyperlinks and therefore respectfully request that the Examiner withdraw the objection to the specification.

Priority

The specification has been amended to add the priority information as suggested by the Examiner in order to comply with 35 U.S.C. § 119(e) and 37 C.F.R. § 1.78. Applicants previously made a proper claim to priority under Article 8 of the Patent Cooperation Treaty.

Objections to the Claims

Claims 210 and 213-216 are objected to because they depend upon non-elected claim 205. Claim 210 has been canceled and claims 213 and 215 have been amended such that they no longer depend on claim 205. Withdrawal of the objections to claims 213, 215, and their dependent claims is therefore respectfully requested.

In addition, the term "naturally occurring," which the Examiner objected to as being grammatically incorrect, no longer appears in any of the claims. Therefore, withdrawal of the objections to claims 215 and 217 is respectfully requested.

Utility Rejections under 35 U.S.C. §101 and §112, First Paragraph

Claims 210-218 and 224-231 have been rejected under 35 U.S.C. §101 and §112, first paragraph, because the claimed invention allegedly "is not supported by either a specific and substantial asserted utility or a well-established utility" (Office Action, page 4). These rejections are traversed.

The rejection of claims 210-218 and 224-231 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in reproductive, gastrointestinal, and nervous system tissues (Specification at Table 3). In particular, similarities between SEQ ID NO:12 and human annexin 31 (g3688370), including the presence of multiple annexin domain signatures, are described in the specification, for example, in Table 2. The specification points out the roles of annexins in phospholipid binding, membrane-cytoskeleton interactions, phospholipase inhibition, anticoagulation, and membrane fusion (Specification at page 4, lines 18-24). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Applicants submit with this paper the Declaration of Dr. Tod Bedilion[1] describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

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[1]The Bedilion Declaration is submitted herewith in unexecuted form. The executed Declaration will be submitted to the Patent office as soon it is available.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed polynucleotide for diagnosis of conditions or diseases characterized by expression of INTRA, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of INTRA for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are

explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Yue '566 application on June 16, 1999 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[2]

In connection with his explanations, Dr. Bedilion states that the "Yue '566 specification would have led a person skilled in the art on June 16, 1999 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:12-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on June 16, 1999] that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

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[2]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Yue '566 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-June 16, 1999 publications showing the state of the art on June 16, 1999. (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on June 16, 1999 (and for several years prior to June 16, 1999) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Yue '566 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Yue '566 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:12-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 16, 1999" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Yue '566 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pp. 33-34 of the Yue '566 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately

would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed in reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (see the Yue '566 application at Table 3), and expresses a protein that is a member of the annexin family known to be associated with diseases such as cancer, immune disorders, neurological disorders, and gastrointestinal disorders, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential cancer, immune disorders, neurological disorders, and gastrointestinal disorders drug candidate or potential toxin with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre-June 16, 1999 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Yue '566 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Yue '566 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999).

In another pre-June 16, 1999 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of the claimed polynucleotide can be imputed based on the relationship between the polypeptide it encodes, INTRA, and another polypeptide of unquestioned utility, annexin 31. The two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to annexin 31. Applicant need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the polypeptide encoded for by the claimed polynucleotide shares more than 97% sequence identity over 345 amino acid residues with annexin 31. This is more than enough homology to demonstrate a reasonable probability that the utility of annexin 31 can be imputed to the claimed invention (through the polypeptide it encodes). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998). Given homology in

excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to annexin 31 is, accordingly, very high.

Members of the annexin family have been implicated in cancer, neurodegenerative diseases, autoimmune diseases, and inflammatory bowel diseases (enclosed references of Bastian (1997) Cell. Mol. Life Sci. 53:554-556; Eberhard et al. (1994) Am. J. Pathol. 145:640-649; and Gerke and Moss (2002) Physiol. Rev. 82:331-371). The phospholipid binding properties of annexins make them potentially useful in radionuclide imaging. For example, annexin V has been used as a marker of apoptosis to monitor the changes in phospholipid distribution that accompany cell death (enclosed references of Blankenberg et al. (1998) Proc. Natl. Acad. Sci. U.S.A. 95:6349-6354 and Blankenberg et al. (2000) Eur. J. Nucl. Med. 27:359-367). Radionuclide imaging with radiolabled annexins may be useful for diagnosis of stroke, neurodegenerative diseases, inflammatory diseases, myocardial ischemia, myelodysplastic disorders, organ transplantation, and cancer.

The Examiner must accept the applicants' demonstration that the homology between the polypeptide encoded for by the claimed invention and annexin 31 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case [Smith et al. (Nat. Biotech 15:1222-1223, 1997); Brenner et al. (Trends in Genetics, 15:132-133, 1999); and Seffernick et al. (J. Bacteriol. 183:2405-2410, 2001]. Most important, none contradicts Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

The Seffernick et al. reference cited by the Examiner does not contradict the findings of Brenner et al. The Seffernick et al. reference describes two enzymes, a melamine deaminase and an

atrazine chlorohydrolase, that are 98% identical, yet have different substrate specificities. These two enzymes belong to a class of bacterial amidohydrolases whose members catalyze the hydrolytic displacement of amino groups or chlorine substituents from triazine ring compounds. Notably, the substrates of the two enzymes, melamine and atrazine, have similar structures except that melamine possesses an amino group and atrazine possesses a chlorine substituent. Some other members of the amidohydrolase superfamily catalyze deamination and dechlorination reactions with both triazine ring substrates. Therefore, the 98% sequence homology between melamine deaminase and atrazine chlorohydrolase correctly predicts their functional similarity and their membership in a common enzyme family. As noted by the Examiner, Seffernick et al. recognize that "functional assignments based on >50% sequence identity are considered to be reasonably sound" (Seffernick et al., page 2409, left column, paragraph 2).

Under the Patent Law, the USPTO must accept the applicant's demonstration that the polypeptide encoded by the claimed invention is a member of the annexin family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The USPTO does not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the USPTO provided any evidence that any member of the annexin family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention, like the other members of the annexin protein family, must be useful.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or

entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific and substantial" utilities. (Office Action at p. 4). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary

skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the

Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the annexin family, the Examiner refused to impute the utility of the members of the annexin family to INTRA. In the Office Action, the Patent Examiner takes the position that, unless Applicants can identify which particular biological function within the class of annexins is possessed by INTRA, utility cannot be imputed. To demonstrate utility by membership in the class of annexins, the Examiner would require that all annexins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses INTRA as if the general class in which it is included is not the annexin family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the annexin family does not. The annexin family is sufficiently specific to rule out any reasonable possibility that INTRA would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the annexin class of proteins has

any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the INTRA encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide also is useful.

It is undisputed that known members of the annexin family are phospholipid binding proteins. A person of ordinary skill in the art need not know any more about how the claimed invention functions to use it, and the Examiner presents no evidence to the contrary. The Examiner then goes on to assume that the only use for INTRA absent knowledge as to how the annexin actually works is further study of INTRA itself.

Not so. As demonstrated by Applicants, knowledge that INTRA is an annexin is more than sufficient to make it useful for the diagnosis and treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders. Indeed, INTRA has been shown to be expressed in reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Specification at Table 3). The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. Because the uses of polynucleotides encoding INTRA in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The PTO rejected the claims at issue on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include uses such as diagnostic assays (e.g., pages 51-56), chromosomal markers (e.g., pages 56-57), and ligand screening assays (e.g., page 36).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training

Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 210, 213-218, and 224-231 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, pages 6-8).

As a preliminary matter, claims 210 and 218 have been canceled. Claim 205, has been amended to remove the biologically active fragment embodiment, which allegedly rendered dependent claims 213-215 indefinite. Therefore, the rejections with respect to these claims are moot.

Claim 216 has been amended as suggested by the Examiner to recite "The method of claim 215."

Claim 217 has been amended as suggested by the Examiner to recite "a polynucleotide completely complementary to a polynucleotide of a)."

Claim 225 has been amended as suggested by the Examiner to delete "the elements" from the term "the elements of the microarray."

Claim 226 and dependent claims 229-231 have been amended as suggested by the Examiner to replace the term "nucleotide molecules" with "nucleic acids."

The Examiner states that claim 226 and dependent claims 227-231 are indefinite because the specification allegedly does not provide a definition for the term "specifically hybridizable." Applicants do not concede to the Patent Office position; however, in the interest of expediting prosecution, claim 226 has been amended to remove the term "specifically hybridizable."

For at least the above reasons, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Written description and enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 210, 213-218, and 224-231 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description and lack of enablement for the claimed genus of polynucleotides. These rejections are respectfully traversed.

As a preliminary matter, claims 210 and 218 have been canceled; therefore, the rejections with respect to these claims are moot. Claim 205 has been amended to remove the variant and fragment embodiments and claim 217 has been amended to remove the variant embodiment. Therefore, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 210, 217, and 218 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Morgan et al. (GenBank Accession Number AJ00985, IDS reference 3). Applicants respectfully traverse the rejection.

Claims 210 and 218 have been canceled; therefore, the rejection with respect to these claims is moot. Claim 217, as currently pending, recites:

> An isolated polynucleotide selected from the group consisting of:
> a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:64,
> b) a polynucleotide completely complementary to a polynucleotide of a), and
> c) an RNA equivalent of a)-b).

Since the reference of Morgan et al. does not disclose the sequence of SEQ ID NO:64, nor a complement of it, withdrawal of the rejection under 35 U.S.C. § 102(a) is respectfully requested.

Claim 218 was rejected under 35 U.S.C. § 102(b) as being anticipated by the reference of Strausberg et al. (GenBank Accession Number AA806217). Since claim 218 has been canceled, the rejection with respect to this claim is moot.

Rejections under 35 U.S.C. § 103

Claims 213-215 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over

Morgan et al. (GenBank Accession Number AJ00985) in view of Morgan et al. (FEBS Letters 434:300-304) on the grounds that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the polynucleotide disclosed by Morgan et al. to insert the nucleic acid of Morgan into an expression vector, transform a host cell with said expression vector, and use said host cell for procuction and purification of ANX31 protein (Office Action, page 14). Claims 224-231 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Morgan et al. (GenBank Accession Number AJ00985) in view of Morgan et al. (FEBS Letters 434:300-304) and Lockhart et al. (U.S. Patent 6,040,138) on the grounds that it would have been obvious to one of ordinary skill in the art at the time the invention was made to us the polynucleotide disclosed by Morgan et al. in microarrays and in methods of generating expression profiles (Office Action, page 15). Claims 224 and 225 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Strausberg et al. in view of Lockhart et al. on the grounds that it would have been obvious to use the nucleotide sequence disclosed by Strausberg et al. to probe the expression pattern of the nucleic acid using an array as taught by Lockhart et al. (Office Action, page 16). These rejections are respectfully traversed for at least the following reasons.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02.

In the present case, the rejection of the claims under 35 U.S.C. § 103(a) is based on the allegation that the references of Morgan et al. or Strausberg et al. disclose polynucleotides that anticipate polynucleotide variants or fragments of SEQ ID NO:64. As mentioned above, claims 205 and 217 have been amended such that they no longer recite variants or fragments. In addition, claims 224 and 226 have also been amended as follows:

> Claim 224. A microarray wherein at least one element of the microarray is a polynucleotide of claim 217.
>
> Claim 226. An array comprising different nucleic acids affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleic acids comprises a first polynucleotide

sequence completely complementary to a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 217.

The pending claims as amended no longer recite variants or fragments of SEQ ID NO:64. Since none of the references cited by the Examiner separately or in combination disclose or suggest the sequences of SEQ ID NO:12 or SEQ ID NO:64, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The following sentence was added immediately after the title of the application on page 1 of the specification:

This application claims benefit under 35 U.S.C. § 119(e) of provisional application 60/139,566, filed on June 16, 1999, provisional application 60/149,640 filed on August 17, 1999, and provisional application 60/164,417 filed on November 9, 1999.

Paragraph beginning at page 17, line 25 and ending on page 11, line 10 has been amended as follows:

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at ncbi.nlm.nih.gov/BLAST/ [http://www.ncbi.nlm.nih.gov/BLAST/]. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at ncbi.nlm.nih.gov/gorf/bl2.html [http://www.ncbi.nlm.nih.gov/gorf/bl2.html]. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50
Expect: 10
Word Size: 11
Filter: on

Paragraph beginning at line 4 of page 62 has been amended as follows:

The genetic map locations of SEQ ID NO:8-14 [fill in the specific SEQ ID NOs if not all of the sequences have been mapped] are described in The Invention as ranges, or intervals, of human chromosomes. [Include the following sentence if any of your sequences have more than one map location.] More than one map location is reported for SEQ ID NO:8-14 [fill in specific SEQ ID NO:s], indicating that previously mapped sequences having similarity, but not complete identity, to SEQ ID NO:8-14 [fill in specific SEQ ID NO:s] were assembled into their respective clusters. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site [(http://www.ncbi.nlm.nih.gov/genemap/),] at ncbi.nlm.nih.gov/genemap/, can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

IN THE CLAIMS:

Claims 210, 218, 227 have been canceled.

Claims 205, 213, 215-217, 224-226, 229-231 have been amended as follows:

205. (Once Amended) An isolated polypeptide [selected from the group consisting of:

a) a polypeptide] comprising an amino acid sequence of SEQ ID NO:12[,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:12,

c) a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:12, and

d) an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:12].

213. (Once Amended) A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim [210] 211.

215. (Once Amended) A method of producing a polypeptide [of claim 205] comprising an amino acid sequence of SEQ ID NO:12, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide [encoding the polypeptide] of claim [205] 211, and

b) recovering the polypeptide so expressed.

216. (Once Amended) [A] The method of claim 215, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO:12.

217. (Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:64,

[b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:64,]

[c)] b) a polynucleotide completely complementary to a polynucleotide of a),

[d) a polynucleotide complementary to a polynucleotide of b),] and

[e)] c) an RNA equivalent of a)-[d)] b).

224. (Once Amended) A microarray wherein at least one element of the microarray is a polynucleotide of claim [218] 217.

225. (Once Amended) A method of generating an expression profile of a sample which contains polynucleotides, the method comprising:

a) labeling the polynucleotides of the sample,

b) contacting the [elements of the] microarray of claim 224 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and

c) quantifying the expression of the polynucleotides in the sample.

226. (Once Amended) An array comprising different [nucleotide molecules] nucleic acids affixed in distinct physical locations on a solid substrate, wherein at least one of said [nucleotide molecules] nucleic acids comprises a first [oligonucleotide or] polynucleotide sequence [specifically hybridizable with at least 30 contiguous nucleotides of] completely complementary to a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 217.

229. (Once Amended) An array of claim 226, further comprising said target polynucleotide hybridized to a [nucleotide molecule] nucleic acid comprising said first [oligonucleotide or] polynucleotide sequence.

230. (Once Amended) An array of claim 226, wherein a linker joins at least one of said [nucleotide molecules] nucleic acids to said solid substrate.

231. (Once Amended) An array of claim 226, wherein each distinct physical location on the substrate contains multiple [nucleotide molecules] nucleic acids, and the multiple [nucleotide molecules] nucleic acids at any single distinct physical location have the same sequence, and each distinct physical location on the substrate contains [nucleotide molecules] nucleic acids having a sequence which differs from the sequence of [nucleotide molecules] nucleic acids at another distinct physical location on the substrate.